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[beta]-(2-Hydroxyphenyl)ethanolamine hydrochloride [2-amino-1-(2-hydroxyphenyl)ethanol hydrochloride]

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Discussion. The molecule has been characterized and the numbering scheme is shown in Fig. 1. Bond lengths and angles involving the non-hydrogen atoms are given in Tables 2 and 3 respectively. A stereoscopic view of the molecule is shown in Fig. 2.

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β-(2-Hydroxyphenyl)ethanolamine Hydrochloride [2-Amino-1-(2-hydroxyphenyl)ethanol Hydrochloride]*

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Abstract. $C_8H_{12}NO_2^+.Cl^-$, m.p. 441–449 K (from ethyl acetate), $P2_12_12_1$, $a = 7{\cdot}363$ (2), $b = 21{\cdot}824$ (6), $c = 5{\cdot}790$ (2) Å, $Z = 4$, $D_x = 1{\cdot}354$, $D_m = 1{\cdot}356$ Mg m^{-3} (flotation: CCl_4–C_6H_6). The structure was solved by *MULTAN*. Full-matrix least-squares refinement converged to $R = 0{\cdot}057$ for the *R* configuration and to $R = 0{\cdot}056$ for the *S* configuration ($P < 0{\cdot}05$). This is consistent with spontaneous resolution of the title compound, single crystals of which provided optically active aqueous solutions. A partially occupied oxygen site O(1)′ is attributed to the oxidation of the alkyl hydroxyl group to a ketone during the data collection. The Cl^- is hydrogen bonded to $H2(N)_{554}$, $H3(N)_{555}$, and $H(O2)_{655}$ (2·37, 2·19, and 2·10 Å). Both O(1) and O(2) are internally hydrogen bonded [H1(N)···O(1), 2·41 and H(O1)···O(2) = 2·24 Å]. Intramolecular hydrogen bonding may account for the unusual pharmacological properties of this compound in which only the N–C(1)–C(2)–O(1) and the O(1)–C(2)–C(3)–C(4) and O(1)–C(2)–C(3)–C(8) torsion angles (−41, −60, +122°) differ significantly from those of other phenylethanolamines.

Introduction. It is generally believed (Iversen, 1967) that, after its release into the circulation, norepinephrine is primarily inactivated through an efficient, specific norepinephrine-uptake process located in the sympathetic nerve terminals. This uptake system has served as a target for the design and the synthesis of compounds (Rotman, Lundstrom, McNeal, Daly & Creveling, 1975) which interfere with the uptake of norepinephrine and thus produce their effects by controlling the amount of this neurotransmitter available in the circulation. A great deal of the research has focused on obtaining information related to the drug structural requirements for interaction with the adrenergic sites of uptake. Such information is necessary for the rational design of drugs that would have a high degree of pharmacological specificity.

Of the compounds tested, the phenylethylamine and phenylethanolamine analogs with hydroxyl substituents in various positions of the aromatic ring have received special attention. Most of these analogs were found (Rotman *et al.*, 1975; Katz, Heller, Jacobson, Rotman & Creveling, 1974) to produce an immediate inhibition of norepinephrine uptake, probably by competing with it for the sites of uptake. However, the *ortho*-hydroxyphenylethanolamines were a striking exception. Unexpectedly, these compounds were all found to have little or no activity as inhibitors of the uptake process (Rotman *et al.*, 1975; Katz *et al.*, 1974) thus raising the possibility that the *o*-hydroxyl group may produce this effect by altering the conformation of the flexible side chain. The *o*-hydroxyl groups are indeed favorably positioned on the phenylethanolamine molecule so that they can easily interact with either one of the functional groups (−OH, $-NH_3$) of the ethanolamine side chain and alter its conformation.

* Steric Requirements for Adrenergic Activity. I.

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This report deals with the crystal structure analysis of the simplest of the above-mentioned inactive phenylethanolamine analogs. It was hoped that a comparison between the structures of the compound in question and those of the previously determined (Carlström, Bergin & Falkenberg, 1973; Paxton & Hamor, 1977) biologically active phenylethanolamines could lead to a better understanding of the sterochemical requirements of the adrenergic site of uptake.

$2\text{-}HOC_6H_4CHOHCH_2NH_3^+Cl^-$ (I) was synthesized from non-asymmetric starting materials (Kappe & Armstrong, 1965; Makriyannis & DiPiro, 1978) yet precession and Weissenberg photographs revealed orthorhombic symmetry, extinctions corresponding to the non-centrosymmetric space group $P2_12_12_1$ and cell volume consistent with $Z = 4$. This suggested that the material had undergone resolution into crystals containing a single enantiomorph without the aid of a resolving agent. A single crystal provided a levorotatory ($-0{\cdot}025 \pm 0{\cdot}002°$) aqueous solution. Another gave a dextrorotatory ($+0{\cdot}008 \pm 0{\cdot}002°$) solution. Measurements were made with a Perkin–Elmer Model 141 Photoelectric Polarimeter at 5896 Å in a 1 ml, 0·1 m cell.

The lattice parameters were refined with a least-squares program using 12 reflections ($30° < 2\theta < 43°$) centered automatically at 296 K on a Picker FACS-I four-circle diffractometer equipped for data collection with Zr-filtered Mo $K\alpha_1$ radiation ($\lambda = 0{\cdot}70930$ Å).

A crystal about 0·2 mm on edge was selected for data collection. Diffraction intensities were automatically collected in the ω-scan mode using 10 s background counts taken at both ends of a 1·4° 2θ offset corrected for dispersion. Of 1291 independent reflections ($2\theta < 54°$), 1018 were considered observable according to the criterion $|F_o| > 3\sigma_F$. Three standard reflections remained constant [$\pm 1{\cdot}02(I)_{av}$] throughout the data collection. Intensity data were corrected for Lorentz and polarization effects. No absorption correction was applied ($\mu = 0{\cdot}373$ mm^{-1}).

Starting with atomic positional parameters generated from the best electron density map produced by *MULTAN* (Germain, Main & Woolfson, 1971), all non-hydrogen atoms were located after several cycles of structure factor calculations, Fourier syntheses and least-squares isotropic refinements (Busing, Martin & Levy, 1962). Full-matrix least-squares anisotropic refinement using a $1/\sigma^2$ weighting scheme, zero-valent scattering factors and corrections for secondary extinction and anomalous dispersion for Cl (*International Tables for X-ray Crystallography*, 1974) converged at $R = 0{\cdot}109$ ($R_w = 0{\cdot}135$). The function minimized was: $\sum w(|F_o| - |F_c|)^2$.

A difference Fourier map revealed one relatively strong peak approximately three times the intensity of each of a series of smaller peaks subsequently identified as H atoms. Initial isotropic temperature factors of 3·0 Å^2 were assigned to H atoms. Least-squares refinement (anisotropic for non-hydrogen atoms) caused the temperature factor of the atom assigned to the strong peak to go strongly negative but with a lower overall R factor. On the basis of the excellent agreement in the experimental and theoretical crystal densities and the intensity of the peak, the presence of solvent or chemical impurity was ruled out.

Based on its location (Fig. 1), the peak was assigned to an O atom [O(1)′] related by partial occupancy to O(1). Occupancy factors were allowed to vary in the final cycles of refinement. Positional parameters for H1(N) and H3(N), which are hydrogen bonded to Cl, failed to refine properly although the atoms were readily discernible in the difference Fourier maps. The parameters for these H atoms were fixed in the final cycles of refinement which converged at $R = 0{\cdot}056$ ($R_w = 0{\cdot}060$).*

Changing the signs of the atomic positional parameters resulted in convergence at $R = 0{\cdot}057$ indicating that the S configuration described by the positional parameters in Table 1 is correct ($P < 0{\cdot}05$) (Hamilton, 1965). Final parameter shifts were less than $0{\cdot}2\sigma$. The final occupancy factors for O(1) and O(1)′ are 0·776 (13) and 0·265 (13), respectively. There were no peaks in the final difference Fourier map greater than 0·2 e Å^{-3}.

Discussion. Bond lengths and angles and pertinent inter- and intramolecular distances are shown in Fig. 2. With the exception of the C(2)–O(1), C(2)–O(1)′ and C(2)–H(C2) bonds (Fig. 2) all bond lengths and angles are consistent with values reported for other phenylethanolamines (Hearn & Bugg, 1972; Paxton & Hamor, 1977; Carlström & Bergin, 1967; Carlström,

* Lists of structure factors and thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 34459 (7 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

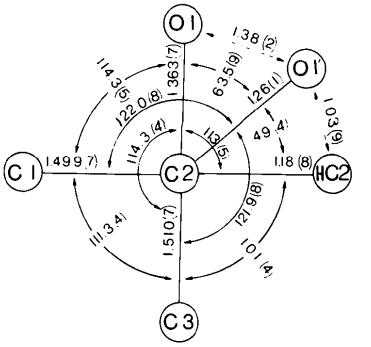

Fig. 1. Local bond distances (Å), angles (°), and interatomic distances and angles about C(2) in β-(2-hydroxyphenyl)ethanolamine hydrochloride.

Table 1. *Positional parameters* ($\times 10^4$; *for* H $\times 10^3$) *in fractions of the lattice translations*

Estimated standard deviations in the last figures are given in parentheses.

	x	*y*	*z*
Cl	1687 (2)	666 (1)	−9585 (2)
O(1)	−3329 (7)	295 (2)	−2798 (9)
O(2)	−5037 (5)	919 (2)	−6640 (8)
N	149 (5)	434 (2)	−4584 (8)
C(1)	−1122 (6)	952 (2)	−4600 (9)
C(2)	−2637 (7)	874 (2)	−2897 (9)
C(3)	−4052 (6)	1370 (2)	−3170 (9)
C(4)	−5207 (6)	1380 (2)	−5082 (9)
C(5)	−6499 (7)	1842 (3)	−5324 (9)
C(6)	−6622 (8)	2291 (3)	−3684 (9)
C(7)	−5488 (8)	2297 (3)	−1811 (9)
C(8)	−4185 (7)	1829 (3)	−1556 (9)
H1(N)	−51*	3*	−466*
H2(N)	65 (6)	43 (2)	−336 (8)
H3(N)	93*	47*	−601*
H1(C1)	−166 (6)	97 (2)	−621 (8)
H2(C1)	−50 (6)	130 (2)	−453 (8)
H(C2)	−192 (9)	102 (4)	−116 (9)
H(C5)	−721 (7)	186 (2)	−676 (9)
H(C6)	−757 (7)	255 (2)	−343 (9)
H(C7)	−551 (8)	265 (3)	−51 (9)
H(C8)	−363 (9)	188 (3)	−11 (9)
H(O1)	−381 (7)	33 (2)	−388 (9)
H(O2)	−587 (8)	90 (3)	−790 (9)
O(1)′	−2420 (20)	589 (8)	−1017 (24)

* Not included in refinement, see text.

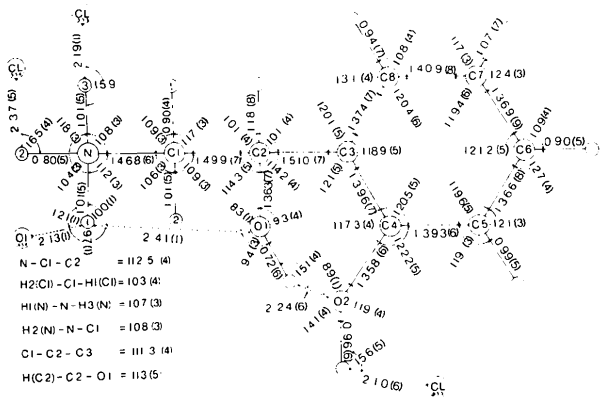

Fig. 2. Bond distances (Å), angles (°), and interatomic distances and angles in β-(2-hydroxyphenyl)ethanolamine hydrochloride.

1973; Phillips, 1954; Bergin, 1971*a*). The C(2)–O(1) bond length (1·363 Å) is significantly shorter than the corresponding bond in other phenylethanolamines (1·40–1·48 Å) while the H(C2)–C(2) bond is longer (1·18 Å). The C(1)–C(2)–H(C2) bond angle (101°) is unusually small. These poorly resolved features may be related to the problem of partial occupancy.

The sum of the C(3)–C(2)–O(1)′, C(1)–C(2)–O(1)′ and C(1)–C(2)–C(3) bond angles (355·2°) is consistent with an sp^2 carbonyl group formed by oxidation of the O(1) hydroxyl group before or during data collection. The fact that the sum of the O(1)–C(2)–O(1)′ and H(C2)–C(2)–O(1)′ bond angles is almost identical to the H(C2)–C(2)–O(1) bond angle (112·4 *vs* 113°) indicates that O(1)′ is also coplanar with H(C2), C(2), and O(1). This is also consistent with the carbonyl hypothesis. The C(2)–O(1)′ bond is longer [1·26(1) Å] than the ketonic bond in adrenalone (1·21 Å) (Bergin, 1971*b*) although aryl ketone bonds of 1·23 Å have been observed in other structures (Ruble, Hite & Soares, 1976).

While the crystallographic and geometric arguments are convincing, we have not been able to demonstrate the presence of a ketone group in the IR spectrum of the crystal used for data collection. Comparison of infrared spectra (KBr disc) of X-ray irradiated (48 h, Mo $K\alpha$) and non-irradiated crystals revealed no absorption in the 1650 cm^{-1} (C=O stretching) region (Stammer, Walton, Wilson, Walker, Trenner, Holly & Folkers, 1958).

An explanation for O(1)′ based on disorder in an enantiomorphically homogeneous or heterogeneous crystal is unlikely since there is no unusual anisotropy in the atoms in this region (Fig. 3). The results of the present analysis show that, in the solid state, the conformation of (I) maintains most of the features observed in other phenylethanolamine salts (Carlström, Bergin & Falkenberg, 1973).

In comparison with octopamine hydrochloride, a representative phenylethanolamine (Paxton & Hamor, 1977), there are three torsion angles which show appreciable variation. In (I), the N–C(1)–C(2)–O(1) and O(1)–C(2)–C(3)–C(8) torsion angles (−41, +122°) are considerably smaller and the O(1)–C(2)–C(3)–C(4) torsion angle (−60°) is considerably larger than the corresponding angles in octopamine, −67, +145 and −39°, respectively. The hydrogen bonding between the alcohol oxygen [O(1)] and one ammonium hydrogen [H1(N)$_{555}$] (O···H = 2·41 Å), a common

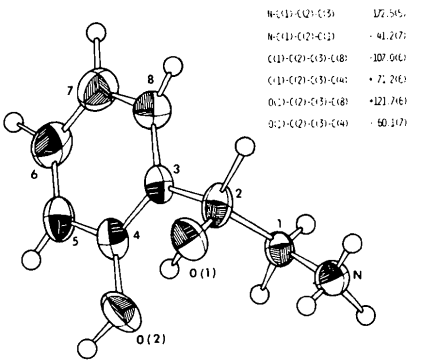

Fig. 3. Thermal-ellipsoid plot including 75% probability for β-(2-hydroxyphenyl)ethanolamine hydrochloride. Torsion angles (°) are for the *R* configuration.

feature in all the phenylethanolamines, is also observed here. The Cl^- ion is hydrogen bonded to $H2(N)_{554}$ (2·37 Å), $H3(N)_{555}$ (2·19 Å), and $H(O2)_{655}$ (2·10 Å). The most prominent new feature in the structure of this compound is the involvement of the alcohol H atom [H(O1)] in an intramolecular hydrogen-bonding interaction with the phenolic O(2) atom (2·24 Å). This interaction may account for the observed distortion in some of the dihedral angles.

The conformation of (I) in the crystal is at variance with results obtained using CNDO calculations (Katz *et al.*, 1974). According to these theoretical calculations, the most stable conformer in analogs of (I) is one in which one N proton is hydrogen bonded to the phenolic O. However, recent studies in our laboratories (Makriyannis & Knittel, 1978) using NMR techniques have provided evidence that the conformation observed in the crystal is also the most stable in solution. The discrepancy in the theoretical calculations may thus be due to an overestimation in the strength of the N–H···O(2) hydrogen bond.

It is tempting to suggest that the hydrogen-bonding interaction of the alcohol proton which is unique for *ortho*-substituted hydroxyphenylethanolamines may also be responsible for the lack of pharmacological activity in these compounds by making the alcohol proton unavailable for interaction with the adrenergic site.

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6,13-Pentacenequinone: Molecular Packing Analysis

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Abstract. $C_{22}H_{12}O_2$, monoclinic, $P2_1/b$, $a = 4·951$ (2), $b = 17·784$ (6), $c = 8·170$ (2) Å, $\gamma = 93·26$ (3)°, $V = 718·2$ (3) Å^3, $Z = 2$, $D_x = 1·42$ Mg m^{-3}. The structure was solved by a molecular-packing analysis and refined by least squares to $R = 0·041$. Apart from the carbonyl groups the molecule is strictly planar. However, the *p*-quinone ring adopts the chair-like form with planar >C=O groups inclined to the molecular plane at angles of 3·1°. The bond lengths and angles closely resemble those in unsubstituted *p*-benzoquinone and napthalene structures. The O atoms exhibit increased thermal anisotropy. This fact is discussed in connection with the observed non-planarity of the central ring.

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